

### 1 **1.14.2.3 Final Labeling Text**

#### 2 **TNKase<sup>®</sup>** 3 **(Tenecteplase)**

#### 4 **DESCRIPTION**

5 TNKase<sup>®</sup> (Tenecteplase) is a tissue plasminogen activator (tPA) produced  
6 by recombinant DNA technology using an established mammalian cell  
7 line (Chinese Hamster Ovary cells). Tenecteplase is a 527 amino acid  
8 glycoprotein developed by introducing the following modifications to the  
9 complementary DNA (cDNA) for natural human tPA: a substitution of  
10 threonine 103 with asparagine, and a substitution of asparagine 117 with  
11 glutamine, both within the kringle 1 domain, and a tetra-alanine  
12 substitution at amino acids 296–299 in the protease domain. Cell culture  
13 is carried out in nutrient medium containing the antibiotic gentamicin  
14 (65 mg/L). However, the presence of the antibiotic is not detectable in the  
15 final product (limit of detection is 0.67 µg/vial). TNKase is a sterile,  
16 white to off-white, lyophilized powder for single intravenous (IV) bolus  
17 administration after reconstitution with Sterile Water for Injection (SWFI),  
18 USP. Each vial of TNKase nominally contains 52.5 mg Tenecteplase,  
19 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20,  
20 which includes a 5% overfill. Each vial will deliver 50 mg of  
21 Tenecteplase.

#### 22 **CLINICAL PHARMACOLOGY**

##### 23 **General**

24 Tenecteplase is a modified form of human tissue plasminogen activator  
25 (tPA) that binds to fibrin and converts plasminogen to plasmin. In the  
26 presence of fibrin, *in vitro* studies demonstrate that Tenecteplase  
27 conversion of plasminogen to plasmin is increased relative to its  
28 conversion in the absence of fibrin. This fibrin specificity decreases  
29 systemic activation of plasminogen and the resulting degradation of  
30 circulating fibrinogen as compared to a molecule lacking this property.  
31 Following administration of 30, 40, or 50 mg of TNKase, there are  
32 decreases in circulating fibrinogen (4%–15%) and plasminogen

33 (11%–24%). The clinical significance of fibrin-specificity on safety  
34 (e.g., bleeding) or efficacy has not been established. Biological potency is  
35 determined by an *in vitro* clot lysis assay and is expressed in  
36 Tenecteplase-specific units. The specific activity of Tenecteplase has  
37 been defined as 200 units/mg.

### 38 **Pharmacokinetics**

39 In patients with acute myocardial infarction (AMI), TNKase administered  
40 as a single bolus exhibits a biphasic disposition from the plasma.  
41 Tenecteplase was cleared from the plasma with an initial half-life of 20 to  
42 24 minutes. The terminal phase half-life of Tenecteplase was 90 to  
43 130 minutes. In 99 of 104 patients treated with Tenecteplase, mean  
44 plasma clearance ranged from 99 to 119 mL/min.

45 The initial volume of distribution is weight related and approximates  
46 plasma volume. Liver metabolism is the major clearance mechanism for  
47 Tenecteplase.

### 48 **CLINICAL STUDIES**

49 ASSENT-2 was an international, randomized, double-blind trial that  
50 compared 30-day mortality rates in 16,949 patients assigned to receive an  
51 IV bolus dose of TNKase or an accelerated infusion of Activase<sup>®</sup>  
52 (Alteplase).<sup>1</sup> Eligibility criteria included onset of chest pain within  
53 6 hours of randomization and ST-segment elevation or left bundle branch  
54 block on electrocardiogram (ECG). Patients were to be excluded from the  
55 trial if they received GP IIb/IIIa inhibitors within the previous 12 hours.  
56 TNKase was dosed using actual or estimated weight in a weight-tiered  
57 fashion as described in [DOSAGE AND ADMINISTRATION](#). All  
58 patients were to receive 150–325 mg of aspirin administered as soon as  
59 possible, followed by 150–325 mg daily. Intravenous heparin was to be  
60 administered as soon as possible: for patients weighing ≤67 kg, heparin  
61 was administered as a 4000 unit IV bolus followed by infusion at  
62 800 U/hr; for patients weighing >67 kg, heparin was administered as a  
63 5000 unit IV bolus followed by infusion at 1000 U/hr. Heparin was

64 continued for 48 to 72 hours with infusion adjusted to maintain aPTT at  
 65 50–75 seconds. The use of GP IIb/IIIa inhibitors was discouraged for the  
 66 first 24 hours following randomization. The results of the primary  
 67 endpoint (30-day mortality rates with non-parametric adjustment for the  
 68 covariates of age, Killip class, heart rate, systolic blood pressure and  
 69 infarct location) along with selected other 30-day endpoints are shown in  
 70 Table 1.

**Table 1**  
**ASSENT-2**  
 Mortality, Stroke, and Combined Outcome of Death or Stroke  
 Measured at Thirty Days

30-Day Events	TNKase (n=8461)	Accelerated Activase (n=8488)	Relative Risk TNKase/Activase (95% CI)
Mortality	6.2%	6.2%	1.00 (0.89, 1.12)
Intracranial Hemorrhage (ICH)	0.9%	0.9%	0.99 (0.73, 1.35)
Any Stroke	1.8%	1.7%	1.07 (0.86, 1.35)
Death or Nonfatal Stroke	7.1%	7.0%	1.01 (0.91, 1.13)

71  
 72 Rates of mortality and the combined endpoint of death or stroke among  
 73 pre-specified subgroups, including age, gender, time to treatment, infarct  
 74 location, and history of previous myocardial infarction, demonstrate  
 75 consistent relative risks across these subgroups. There was insufficient  
 76 enrollment of non-Caucasian patients to draw any conclusions regarding  
 77 relative efficacy in racial subsets.

78 Rates of in-hospital procedures, including percutaneous transluminal  
 79 coronary angioplasty (PTCA), stent placement, intra-aortic balloon pump  
 80 (IABP) use, and coronary artery bypass graft (CABG) surgery, were  
 81 similar between the TNKase and Activase<sup>®</sup> (Alteplase) groups.

82 TIMI 10B was an open-label, controlled, randomized, dose-ranging,  
 83 angiography study which utilized a blinded core laboratory for review of  
 84 coronary arteriograms.<sup>2</sup> Patients (n=837) presenting within 12 hours of  
 85 symptom onset were treated with fixed doses of 30, 40, or 50 mg of  
 86 TNKase or the accelerated infusion of Activase and underwent coronary  
 87 arteriography at 90 minutes. The results showed that the 40 mg and 50 mg  
 88 doses were similar to accelerated infusion of Activase in restoring  
 89 patency. TIMI Grade 3 flow and TIMI Grade 2/3 flow at 90 minutes are  
 90 shown in Table 2. The exact relationship between coronary artery patency  
 91 and clinical activity has not been established.

**Table 2**  
 TIMI 10B Patency Rates  
 TIMI Grade Flow at 90 Minutes

	Activase ≤100 mg (n=311)	TNKase 30 mg (n=302)	TNKase 40 mg (n=148)	TNKase 50 mg (n=76)
TIMI Grade 3 Flow	63%	54%	63%	66%
TIMI Grade 2/3 Flow	82%	77%	79%	88%
95% CI (TIMI 2/3 Flow)	(77%,86%)	(72%,81%)	(72%,85%)	(79%,94%)

92  
 93 The angiographic results from TIMI 10B and the safety data from  
 94 ASSENT-1, an additional uncontrolled safety study of 3,235  
 95 TNKase-treated patients, provided the framework to develop a  
 96 weight-tiered TNKase dose regimen.<sup>3</sup> Exploratory analyses suggested that  
 97 a weight-adjusted dose of 0.5 mg/kg to 0.6 mg/kg of TNKase resulted in a  
 98 better patency to bleeding relationship than fixed doses of TNKase across  
 99 a broad range of patient weights.

100 The Assessment of the Safety and Efficacy of a New Treatment Strategy  
 101 with Percutaneous Coronary Intervention (ASSENT 4 PCI) was a  
 102 Phase IIIb/IV study designed to assess the safety and effectiveness of a  
 103 strategy of administering full dose TNKase with a single bolus of 4000 U

104 of unfractionated heparin in patients with ST segment elevation AMI, in  
105 whom primary percutaneous coronary intervention (PCI) was planned, but  
106 in whom a delay of 1-3 hours was anticipated before PCI. The trial was  
107 prematurely terminated with 1667 randomized patients (75 of whom were  
108 treated in the United States) due to a numerically higher mortality in the  
109 patients receiving TNKase prior to primary PCI versus PCI without  
110 TNKase (median time from randomization to balloon of 115 minutes).  
111 The incidence of the 90-day primary endpoint, a composite of death or  
112 cardiogenic shock or congestive heart failure (CHF) within 90 days, was  
113 18.6% in patients treated with TNKase plus PCI versus 13.4% in those  
114 treated with PCI alone ( $p = 0.0055$ ; OR 1.39 (95% C.I. 1.11–1.74)).

115 There were trends toward worse outcomes in the individual components of  
116 the primary endpoint between TNKase plus PCI versus PCI alone  
117 (mortality 6.7% vs. 5.0%, respectively; cardiogenic shock 6.1% vs. 4.8%,  
118 respectively; and CHF 12.1% vs. 9.4%, respectively). In addition, there  
119 were trends towards worse outcomes in recurrent MI (6.1% vs. 3.5%,  
120 respectively;  $p=0.03$ ) and repeat target vessel revascularization (6.6% vs.  
121 3.6%, respectively;  $p=0.005$ ) in patients receiving TNKase plus PCI  
122 versus PCI alone.

123 There was no difference in in-hospital major bleeding between the two  
124 groups (5.6% vs. 4.4% for TNKase plus PCI vs. PCI alone, respectively).  
125 For patients treated with TNKase plus PCI, in-hospital rates of intracranial  
126 hemorrhage and total stroke were similar to those observed in previous  
127 trials (0.97% and 1.8%, respectively); however, none of the patients  
128 treated with PCI alone experienced a stroke (ischemic, hemorrhagic or  
129 other).

### 130 **INDICATIONS AND USAGE**

131 TNKase<sup>®</sup> (Tenecteplase) is indicated for use in the reduction of mortality  
132 associated with acute myocardial infarction (AMI). Treatment should be  
133 initiated as soon as possible after the onset of AMI symptoms  
134 (see [CLINICAL STUDIES](#)).

135 **CONTRAINDICATIONS**

136 **TNKase therapy in patients with acute myocardial infarction is**  
137 **contraindicated in the following situations because of an increased**  
138 **risk of bleeding (see WARNINGS):**

- 139 • **Active internal bleeding**
- 140 • **History of cerebrovascular accident**
- 141 • **Intracranial or intraspinal surgery or trauma within 2 months**
- 142 • **Intracranial neoplasm, arteriovenous malformation, or aneurysm**
- 143 • **Known bleeding diathesis**
- 144 • **Severe uncontrolled hypertension**

145 **WARNINGS**

146 **Bleeding**

147 The most common complication encountered during TNKase therapy is  
148 bleeding. The type of bleeding associated with thrombolytic therapy can  
149 be divided into two broad categories:

- 150 • Internal bleeding, involving intracranial and retroperitoneal sites, or  
151 the gastrointestinal, genitourinary, or respiratory tracts.
- 152 • Superficial or surface bleeding, observed mainly at vascular puncture  
153 and access sites (e.g., venous cutdowns, arterial punctures) or sites of  
154 recent surgical intervention.

155 Should serious bleeding (not controlled by local pressure) occur, any  
156 concomitant heparin or antiplatelet agents should be discontinued  
157 immediately.

158 In clinical studies of TNKase, patients were treated with both aspirin and  
159 heparin. Heparin may contribute to the bleeding risks associated with  
160 TNKase. The safety of the use of TNKase with other antiplatelet agents  
161 has not been adequately studied (see PRECAUTIONS: [Drug Interactions](#)).  
162 Intramuscular injections and nonessential handling of the patient should be  
163 avoided for the first few hours following treatment with TNKase.  
164 Venipunctures should be performed and monitored carefully.

165 Should an arterial puncture be necessary during the first few hours  
166 following TNKase therapy, it is preferable to use an upper extremity  
167 vessel that is accessible to manual compression. Pressure should be  
168 applied for at least 30 minutes, a pressure dressing applied, and the  
169 puncture site checked frequently for evidence of bleeding.

170 Each patient being considered for therapy with TNKase should be  
171 carefully evaluated and anticipated benefits weighed against potential risks  
172 associated with therapy. In the following conditions, the risk of TNKase  
173 therapy may be increased and should be weighed against the anticipated  
174 benefits:

- 175 • Recent major surgery, e.g., coronary artery bypass graft, obstetrical  
176 delivery, organ biopsy, previous puncture of noncompressible vessels
- 177 • Cerebrovascular disease
- 178 • Recent gastrointestinal or genitourinary bleeding
- 179 • Recent trauma
- 180 • Hypertension: systolic BP  $\geq$  180 mm Hg and/or diastolic  
181 BP  $\geq$  110 mm Hg
- 182 • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial  
183 fibrillation
- 184 • Acute pericarditis
- 185 • Subacute bacterial endocarditis
- 186 • Hemostatic defects, including those secondary to severe hepatic or  
187 renal disease
- 188 • Severe hepatic dysfunction
- 189 • Pregnancy
- 190 • Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic  
191 conditions
- 192 • Septic thrombophlebitis or occluded AV cannula at seriously infected  
193 site
- 194 • Advanced age (see PRECAUTIONS: [Geriatric Use](#))
- 195 • Patients currently receiving oral anticoagulants, e.g., warfarin sodium

- 196 • Recent administration of GP IIb/IIIa inhibitors  
197 • Any other condition in which bleeding constitutes a significant hazard  
198 or would be particularly difficult to manage because of its location

### 199 **Cholesterol Embolization**

200 Cholesterol embolism has been reported rarely in patients treated with all  
201 types of thrombolytic agents; the true incidence is unknown. This serious  
202 condition, which can be lethal, is also associated with invasive vascular  
203 procedures (e.g., cardiac catheterization, angiography, vascular surgery)  
204 and/or anticoagulant therapy. Clinical features of cholesterol embolism  
205 may include livedo reticularis, “purple toe” syndrome, acute renal failure,  
206 gangrenous digits, hypertension, pancreatitis, myocardial infarction,  
207 cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel  
208 infarction, and rhabdomyolysis.

### 209 **Arrhythmias**

210 Coronary thrombolysis may result in arrhythmias associated with  
211 reperfusion. These arrhythmias (such as sinus bradycardia, accelerated  
212 idioventricular rhythm, ventricular premature depolarizations, ventricular  
213 tachycardia) are not different from those often seen in the ordinary course  
214 of acute myocardial infarction and may be managed with standard  
215 anti-arrhythmic measures. It is recommended that anti-arrhythmic therapy  
216 for bradycardia and/or ventricular irritability be available when TNKase is  
217 administered.

### 218 **Use with Percutaneous Coronary Intervention (PCI)**

219 In patients with large ST segment elevation myocardial infarction,  
220 physicians should choose either thrombolysis or PCI as the primary  
221 treatment strategy for reperfusion. Rescue PCI or subsequent elective PCI  
222 may be performed after administration of thrombolytic therapies if  
223 medically appropriate; however, the optimal use of adjunctive  
224 antithrombotic and antiplatelet therapies in this setting is unknown.

**225 PRECAUTIONS****226 General**

227 Standard management of myocardial infarction should be implemented  
228 concomitantly with TNKase treatment. Arterial and venous punctures  
229 should be minimized. Noncompressible arterial puncture must be avoided  
230 and internal jugular and subclavian venous punctures should be avoided to  
231 minimize bleeding from the noncompressible sites. In the event of serious  
232 bleeding, heparin and antiplatelet agents should be discontinued  
233 immediately. Heparin effects can be reversed by protamine.

**234 Readministration**

235 Readministration of plasminogen activators, including TNKase, to patients  
236 who have received prior plasminogen activator therapy has not been  
237 systematically studied. Three of 487 patients tested for antibody  
238 formation to TNKase had a positive antibody titer at 30 days. The data  
239 reflect the percentage of patients whose test results were considered  
240 positive for antibodies to TNKase in a radioimmunoprecipitation assay,  
241 and are highly dependent on the sensitivity and specificity of the assay.  
242 Additionally, the observed incidence of antibody positivity in an assay  
243 may be influenced by several factors including sample handling,  
244 concomitant medications, and underlying disease. For these reasons,  
245 comparison of the incidence of antibodies to TNKase with the incidence  
246 of antibodies to other products may be misleading. Although sustained  
247 antibody formation in patients receiving one dose of TNKase has not been  
248 documented, readministration should be undertaken with caution. If an  
249 anaphylactic reaction occurs, appropriate therapy should be administered.

**250 Drug Interactions**

251 Formal interaction studies of TNKase with other drugs have not been  
252 performed. Patients studied in clinical trials of TNKase were routinely  
253 treated with heparin and aspirin. Anticoagulants (such as heparin and  
254 vitamin K antagonists) and drugs that alter platelet function (such as  
255 acetylsalicylic acid, dipyridamole, and GP IIb/IIIa inhibitors) may increase

256 the risk of bleeding if administered prior to, during, or after TNKase  
257 therapy.

### 258 **Drug/Laboratory Test Interactions**

259 During TNKase therapy, results of coagulation tests and/or measures of  
260 fibrinolytic activity may be unreliable unless specific precautions are  
261 taken to prevent *in vitro* artifacts. Tenecteplase is an enzyme that, when  
262 present in blood in pharmacologic concentrations, remains active under  
263 *in vitro* conditions. This can lead to degradation of fibrinogen in blood  
264 samples removed for analysis.

### 265 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

266 Studies in animals have not been performed to evaluate the carcinogenic  
267 potential, mutagenicity, or the effect on fertility.

### 268 **Pregnancy (Category C)**

269 TNKase has been shown to elicit maternal and embryo toxicity in rabbits  
270 given multiple IV administrations. In rabbits administered 0.5, 1.5, and  
271 5.0 mg/kg/day, vaginal hemorrhage resulted in maternal deaths.  
272 Subsequent embryonic deaths were secondary to maternal hemorrhage and  
273 no fetal anomalies were observed. TNKase does not elicit maternal and  
274 embryo toxicity in rabbits following a single IV administration. Thus, in  
275 developmental toxicity studies conducted in rabbits, the no observable  
276 effect level (NOEL) of a single IV administration of TNKase on maternal  
277 or developmental toxicity was 5 mg/kg (approximately 8–10 times the  
278 human dose). There are no adequate and well-controlled studies in  
279 pregnant women. TNKase should be given to pregnant women only if the  
280 potential benefits justify the potential risk to the fetus.

### 281 **Nursing Mothers**

282 It is not known if TNKase is excreted in human milk. Because many  
283 drugs are excreted in human milk, caution should be exercised when  
284 TNKase is administered to a nursing woman.

**285 Pediatric Use**

286 The safety and effectiveness of TNKase in pediatric patients have not been  
287 established.

**288 Geriatric Use**

289 Of the patients in ASSENT-2 who received TNKase, 4,958 (59%) were  
290 under the age of 65; 2,256 (27%) were between the ages of 65 and 74; and  
291 1,244 (15%) were 75 and over. The 30-day mortality rates by age were  
292 2.5% in patients under the age of 65, 8.5% in patients between the ages of  
293 65 and 74, and 16.2% in patients age 75 and over. The ICH rates were  
294 0.4% in patients under the age of 65, 1.6% in patients between the ages of  
295 65 and 74, and 1.7% in patients age 75 and over. The rates of any stroke  
296 were 1.0% in patients under the age of 65, 2.9% in patients between the  
297 ages of 65 and 74, and 3.0% in patients age 75 and over. Major bleeding  
298 rates, defined as bleeding requiring blood transfusion or leading to  
299 hemodynamic compromise, were 3.1% in patients under the age of 65,  
300 6.4% in patients between the ages of 65 and 74, and 7.7% in patients  
301 age 75 and over. In elderly patients, the benefits of TNKase on mortality  
302 should be carefully weighed against the risk of increased adverse events,  
303 including bleeding.

**304 ADVERSE REACTIONS****305 Bleeding**

306 The most frequent adverse reaction associated with TNKase is bleeding  
307 (see [WARNINGS](#)).

308 Should serious bleeding occur, concomitant heparin and antiplatelet  
309 therapy should be discontinued. Death or permanent disability can occur  
310 in patients who experience stroke or serious bleeding episodes.

311 For TNKase-treated patients in ASSENT-2, the incidence of intracranial  
312 hemorrhage was 0.9% and any stroke was 1.8%. The incidence of all  
313 strokes, including intracranial bleeding, increases with increasing age  
314 (see PRECAUTIONS: [Geriatric Use](#)).

315 In the ASSENT-2 study, the following bleeding events were reported  
316 (see Table 3).

**Table 3**  
ASSENT-2  
Non-ICH Bleeding Events

	TNKase (n=8461)	Accelerated Activase (n=8488)	Relative Risk for TNKase/Activase (95% CI)
Major bleeding <sup>a</sup>	4.7%	5.9%	0.78 (0.69, 0.89)
Minor bleeding	21.8%	23.0%	0.94 (0.89, 1.00)
Units of transfused blood			
Any	4.3%	5.5%	0.77 (0.67, 0.89)
1-2	2.6%	3.2%	
>2	1.7%	2.2%	

<sup>a</sup> Major bleeding is defined as bleeding requiring blood transfusion or leading to hemodynamic compromise.

317

318 Non-intracranial major bleeding and the need for blood transfusions were  
319 lower in patients treated with TNKase.

320 Types of major bleeding reported in 1% or more of the patients were  
321 hematoma (1.7%) and gastrointestinal tract (1%). Types of major  
322 bleeding reported in less than 1% of the patients were urinary tract,  
323 puncture site (including cardiac catheterization site), retroperitoneal,  
324 respiratory tract, and unspecified. Types of minor bleeding reported in 1%  
325 or more of the patients were hematoma (12.3%), urinary tract (3.7%),  
326 puncture site (including cardiac catheterization site) (3.6%), pharyngeal  
327 (3.1%), gastrointestinal tract (1.9%), epistaxis (1.5%), and unspecified  
328 (1.3%).

### 329 **Allergic Reactions**

330 Allergic-type reactions (e.g., anaphylaxis, angioedema, laryngeal edema,  
331 rash, and urticaria) have rarely (<1%) been reported in patients treated  
332 with TNKase. Anaphylaxis was reported in <0.1% of patients treated  
333 with TNKase; however, causality was not established. When such  
334 reactions occur, they usually respond to conventional therapy.

335 **Other Adverse Reactions**

336 The following adverse reactions have been reported among patients  
 337 receiving TNKase in clinical trials. These reactions are frequent sequelae  
 338 of the underlying disease, and the effect of TNKase on the incidence of  
 339 these events is unknown.

340 These events include cardiogenic shock, arrhythmias, atrioventricular  
 341 block, pulmonary edema, heart failure, cardiac arrest, recurrent myocardial  
 342 ischemia, myocardial reinfarction, myocardial rupture, cardiac tamponade,  
 343 pericarditis, pericardial effusion, mitral regurgitation, thrombosis,  
 344 embolism, and electromechanical dissociation. These events can be  
 345 life-threatening and may lead to death. Nausea and/or vomiting,  
 346 hypotension, and fever have also been reported.

347 **DOSAGE AND ADMINISTRATION**

348 **Dosage**

349 TNKase<sup>®</sup> (Tenecteplase) is for intravenous administration only. The  
 350 recommended total dose should not exceed 50 mg and is based upon  
 351 patient weight.

352 A single bolus dose should be administered over 5 seconds based on  
 353 patient weight. Treatment should be initiated as soon as possible after the  
 354 onset of AMI symptoms (see [CLINICAL STUDIES](#)).

Dose Information Table

Patient Weight (kg)	TNKase (mg)	Volume TNKase* to be administered (mL)
<60	30	6
≥60 to <70	35	7
≥70 to <80	40	8
≥80 to <90	45	9
≥90	50	10

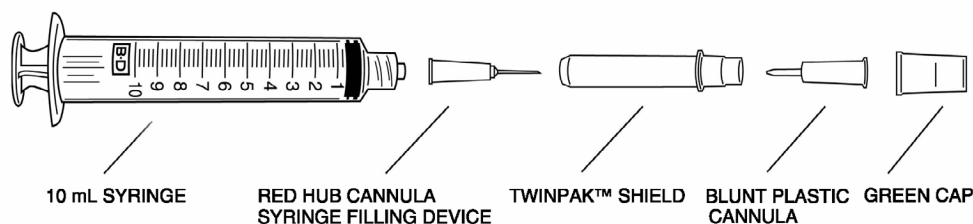
\*From one vial of TNKase reconstituted with 10 mL SWFI.

355

356 The safety and efficacy of TNKase have only been investigated with  
 357 concomitant administration of heparin and aspirin as described in  
 358 [CLINICAL STUDIES](#).

359

360 The **B-D**<sup>®</sup> 10 mL Syringe with TwinPak<sup>™</sup> Dual Cannula Device



361

362

### 363 **Reconstitution**

364 NOTE: Read all instructions completely before beginning reconstitution  
 365 and administration.

366 1. Remove the shield assembly from the supplied B-D<sup>®</sup> 10 mL syringe  
 367 with TwinPak<sup>™</sup> Dual Cannula Device (see figure) and aseptically  
 368 withdraw 10 mL of Sterile Water for Injection (SWFI), USP, from the  
 369 supplied diluent vial using the red hub cannula syringe filling device.  
 370 Do not use Bacteriostatic Water for Injection, USP.

371 Note: Do not discard the shield assembly.

372 2. Inject the entire contents of the syringe (10 mL) into the TNKase vial  
 373 directing the diluent stream into the powder. Slight foaming upon  
 374 reconstitution is not unusual; any large bubbles will dissipate if the  
 375 product is allowed to stand undisturbed for several minutes.

376 3. Gently swirl until contents are completely dissolved. DO NOT  
 377 SHAKE. The reconstituted preparation results in a colorless to pale  
 378 yellow transparent solution containing TNKase at 5 mg/mL at a pH of  
 379 approximately 7.3. The osmolality of this solution is approximately  
 380 290 mOsm/kg.

381 4. Determine the appropriate dose of TNKase (see [Dose Information](#)  
 382 [Table](#)) and withdraw this volume (in milliliters) from the reconstituted  
 383 vial with the syringe. **Any unused solution should be discarded.**

- 384 5. Once the appropriate dose of TNKase is drawn into the syringe, stand  
385 the shield vertically on a flat surface (with green side down) and  
386 passively recap the red hub cannula.
- 387 6. Remove the entire shield assembly, including the red hub cannula, by  
388 twisting counterclockwise. Note: The shield assembly also contains  
389 the clear-ended blunt plastic cannula; retain for split septum IV  
390 access.

### 391 **Administration**

- 392 1. The product should be visually inspected prior to administration for  
393 particulate matter and discoloration. TNKase may be administered as  
394 reconstituted at 5 mg/mL.
- 395 2. Precipitation may occur when TNKase is administered in an IV line  
396 containing dextrose. Dextrose-containing lines should be flushed  
397 with a saline-containing solution prior to and following single bolus  
398 administration of TNKase.
- 399 3. Reconstituted TNKase should be administered as a single IV bolus  
400 over 5 seconds.
- 401 4. Because TNKase contains no antibacterial preservatives, it should be  
402 reconstituted immediately before use. If the reconstituted TNKase is  
403 not used immediately, refrigerate the TNKase vial at 2–8°C  
404 (36–46°F) and use within 8 hours.
- 405 5. Although the supplied syringe is compatible with a conventional  
406 needle, this syringe is designed to be used with needleless IV systems.  
407 From the information below, follow the instructions applicable to the  
408 IV system in use.

- Split septum IV system:**
- Remove the green cap.
  - Attach the clear-ended blunt plastic cannula to the syringe.
  - Remove the shield and use the blunt plastic cannula to access the split septum injection port.
  - Because the blunt plastic cannula has two side ports, air or fluid expelled through the cannula will exit in two sideways directions; direct away from face or mucous membranes.

**Luer-Lok<sup>®</sup> system:** Connect syringe directly to IV port.

**Conventional needle (not supplied in this kit):** Attach a large bore needle, e.g., 18 gauge, to the syringe's universal Luer-Lok<sup>®</sup>.

409

410 6. Dispose of the syringe, cannula and shield per established procedures.

411 **HOW SUPPLIED**

412 TNKase<sup>®</sup> (Tenecteplase) is supplied as a sterile, lyophilized powder in a  
413 50 mg vial under partial vacuum. Each 50 mg vial of TNKase is packaged  
414 with one 10 mL vial of Sterile Water for Injection, USP for reconstitution,  
415 the B-D<sup>®</sup> 10 mL syringe with TwinPak<sup>™</sup> Dual Cannula Device, and three  
416 alcohol prep pads. NDC 50242-038-61.

417 **Stability and Storage**

418 Store lyophilized TNKase at controlled room temperature not to exceed  
419 30°C (86°F) or under refrigeration 2–8°C (36–46°F). Do not use beyond  
420 the expiration date stamped on the vial.

421 **REFERENCES**

- 422 1. ASSENT-2 Investigators. Single-bolus tenecteplase compared with  
 423 front-loaded alteplase in acute myocardial infarction: the  
 424 ASSENT-2 double-blind randomised trial.  
 425 *Lancet* 1999;354:716–22.
- 426 2. Cannon CP, Gibson CM, McCabe CH, Adgey AAJ, Schweiger MJ,  
 427 Sequeira RF, et al. TNK-tissue plasminogen activator compared  
 428 with front-loaded alteplase in acute myocardial infarction. Results  
 429 of the TIMI 10B trial. *Circulation* 1998;98:2805–14.
- 430 3. Van de Werf F, Cannon CP, Luyten A, Houbracken K,  
 431 McCabe CH, Berioli S, et al. Safety assessment of a single bolus  
 432 administration of TNK tissue- plasminogen activator in acute  
 433 myocardial infarction: the ASSENT-1 trial.  
 434 *Am Heart J* 1999;137:786–91.

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